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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/666,022	09/17/2003	Dennis M. Klinman	4239-66899	7954

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EXAMINER

HORNING, MICHELLE S

ART UNIT	PAPER NUMBER
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1648

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/666,022	Applicant(s) KLINMAN ET AL.	
	Examiner MICHELLE HORNING	Art Unit 1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 13 July 2010.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,4-6,8-14,18-21,25-27,29,31 and 35-39 is/are pending in the application.
- 4a) Of the above claim(s) 31,35,37 and 39 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,4-6,8-14,18-21,25-27,29,36 and 38 is/are rejected.
- 7) ☒ Claim(s) 19, 20 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

This action is responsive to communication filed 7/13/2010.

Claims 1, 4-6, 8-14, 18-21, 25-27, 29, 36 and 38 are under current examination.

Claims 31, 35, 37 and 39 are withdrawn. Note that these claims are directed to the sequence set forth by SEQ ID NO: 178 and this sequence is structurally distinct from that of SEQ ID NOs: 1 (elected species) and 177.

Any rejection(s) and/or objection(s) not reiterated herein have been withdrawn.

Claim Objections-NECESSITATED BY AMENDMENTS

Claims 19 and 20 are objected to because of the following informalities: Claims 19 and 20 are dependent on a cancelled claim. Appropriate correction is required.

For purposes of examination, the claims will be read as if they depend from claim 4.

Claim Rejections - 35 USC § 103-NECESSITATED BY AMENDMENTS

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

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Claims 1, 4-6, 8-14, 18-21, 25-27, 29, 36 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klinman (WO/0061151-previously cited; see IDS), Cho et al. (*Nature Biotechnology*, 2000-previously cited; see IDS), Alvar et al. (*Clinical Microbiology Reviews*, 1997-see attached 892) and de la Rosa et al (*J. of Clinical Microbiology*, 2002-see attached 892).

The claims are drawn to (in part): a method of increasing an immune response to an opportunistic infection in an immunocompromised subject comprising:

Selecting an immunocompromised subject infected with a secondary infection, wherein the immunocompromised subject is immunocompromised as a result of an infection with HIV or SIV, and wherein the secondary infection is infection with *Leishmania*;

Administering to the immunocompromised subject infected with the secondary infection a therapeutically effective amount of an immunostimulatory D ODN, wherein the D ODN is at least 18 nucleotides to about 30 nucleotides in length and comprises a sequence represented by the following formula:

5'-X1 X2 X3 Pu1 Py2 CpG Pu3 Py4 X4 X5 X6 (W)M (G)N-3' wherein the central CpG motif is unmethylated, Pu is a purine, Py is a pyrimidine, X and W are any nucleotide, M is any integer from 0 to 10, and N is any integer from 4 to 10; and

Assessing the immune response to the *Leishmania* in the subject;

Thereby increasing the response to the *Leishmania* in the immunocompromised subject.

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Klinman teaches a method of increasing an immune response in a subject using an immunostimulatory D oligonucleotide wherein the sequence is represented by the following formula: 5'-X1 X2 X3 Pu1 Py2 CpG Pu3 Py4 X4 X5 X6 (W)M (G)N-3' wherein the central CpG motif is unmethylated (see Abstract and SEQ ID NO: 37 which fits this formula; see instant claim 1, *in part*). Note that the sequence set forth by SEQ ID NO: 37 of this prior art reference is as follows: ggtgcatcgatgcagggggg and this sequence meets the structural limitations of instant claim 8 and instant claims 21, 26, 27, 29, 36 and 38 (for both SEQ ID NO: 1 and SEQ ID NO: 177 of the instant specification). The author also discloses the use of a phosphorothioate which may occur at either termini of a sequence, including the last two or three 5' and/or 3' nucleotides (p. 3, lines 26+, p. 10, lines 7+, p. 14, lines 1+ and instant claims 12 and 13). Note that the phosphodiester bases as claimed in claims 9-11 are normal DNA phosphodiesterase linkages, i.e. without modifications (p. 13, line 12). Also see claim 3 of this reference, claiming a sequence wherein the sequence on the 5' side of the CpG sequence forms a palindrome with the sequence on the 3' side of the CpG sequence. This meets the structural limitation of claim 14 wherein X1X2X3Pu1Py2 and Pu3Py4X4X5X6 are self-complementary. Tables 1-3 provide the functional characterization of the sequences in the induction of an immune response. The author states that the disclosed invention can be used to treat prevent or ameliorate any suitable disease associated with the immune system, such as immune system deficiencies which include those diseases or disorders in which the immune system is not functioning at normal capacity, or in which it would be useful to boost the immune system response (p. 8, lines 19+).

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While Klinman teaches the structure of the immunostimulatory sequence as claimed and administration of such in order to boost the immune system response in an immune system that is not functioning at normal capacity, Klinman does not teach a method of increasing an immune response to an *opportunistic infection in an immunocompromised subject having HIV-1, HIV-2 or AIDS wherein the secondary infection is a Leishmania infection.*

Cho et al. describes the use of immunostimulatory DNA sequences containing unmethylated CpG motifs for stimulating host defense in subjects with chronic immunosuppression and AIDS (see abstract). Cho et al. provide that immunostimulatory DNA sequence-based vaccines have a clinical application in AIDS and other immunodeficiencies and these vaccines may provide protection against opportunistic infection (see p. 513, col. 1).

Alvar et al. describe *Leishmania* as opportunistic pathogens that infect patients with either HIV-1 or HIV-2 (p. 299, col. 2 and p. 312, col. 2; instant claims 4 and 5).

De la Rosa et al. teach that *Leishmania* occurs in HIV-1 infected patients and AIDS-related disorder (see introduction and claims 4 and 6). De la Rosa et al. teaches that HAART has a protective effective on the development of *Leishmania* in HIV-infected patients (whole document). The authors disclose that HAART therapy may provide a major impact in countries where HIV-*Leishmania* co-infection is endemic, because *Leishmania* causes morbidity and mortality by itself and enhances the effect of HIV infection in HIV-seropositive patients (see p. 766, col. 2, para. 1 and Table 2, p. 764

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disclosing AZT as a anti-retroviral drug of the HAART regimen; see instant claims 18-20).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the CpG-containing sequences described by Klinman in a method for treating selected immunocompromised subjects with a *Leishmania* infection and assessing the resulting responses. One of ordinary skill in the art at the time the invention was made would have been motivated to use a characterized immunostimulatory CpG sequence (as taught by Klinman) for the advantage of stimulating a host defense in AIDS or HIV-associated immunosuppression. Separately, Klinman teaches that the disclosed methods could be used when the immune system is not functioning at normal capacity, or in which it would be useful to boost the immune system response (p. 8, lines 19+) and this would motivate one of ordinary skill in the art to select immunocompromised subjects, including those with a secondary infection, such as *Leishmania*. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success given the underlying techniques (i.e. making and administering CpG-containing sequences) are commonly known and widely used in the prior art by one of ordinary skill in the art.

It would have been obvious to one of ordinary skill in the art at the time of the invention to also use HAART therapy in combination with CpG-containing sequences described by Klinman in a method for treating selected HIV-immunocompromised subjects with a *Leishmania* infection and assessing the resulting responses. One would have been motivated to do so because HAART is a known antiretroviral therapy for HIV

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and the prior art discloses that HAART has a protective effect against *Leishmania* in patients that are co-infected with *Leishmania* and HIV; see results by de la Rosa which provides a reasonable expectation of success

The invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicant's arguments with respect to claims 1, 4-6, 8-14, 18-21, 25-27, 29, 36 and 38 have been considered but are moot in view of the new ground(s) of rejection.

Applicant argues that the case of obviousness is overcome due to an unexpected superior result and points to the Declaration filed on June 5, 2008. It is noted that Applicant provides a limited example of results (SIV-infected macaques further infected with *L. major*) and this example is not commensurate with the scope of the claimed invention. Separately noted is that the Declaration provide results of the claimed invention (e.g. decrease in parasite burden, etc.); however, it is not clear how the results are superior.

Conclusion

No claim is allowed at this time.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MICHELLE HORNING whose telephone number is (571)272-9036. The examiner can normally be reached on Monday-Friday 8:00-5:00 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ZACHARIAH LUCAS can be reached on 571-272-0905. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/M. H./
Examiner, Art Unit 1648

/Zachariah Lucas/
Supervisory Patent Examiner, Art Unit 1648